Risk of cancer in children with the diagnosis immaturity at birth

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Summary

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Cancer risk in children born before term has been assessed in a large number of case–control studies but very rarely in cohort studies. We carried out a cohort study of 35 178 children with the diagnosis immaturity at birth in the Hospital Discharge Register during 1977–89. The children were followed for cancer in the Danish Cancer Registry until 1994 and comparisons were made with incidence rates for all children in Denmark. The 64 observed cases of childhood cancer in the cohort corresponded closely to the expected number {standardised incidence ratio (SIR) = 1.03; [95% confidence interval (CI) 0.80, 1.32]}. The only cancer site with an observed number that deviated significantly from the expected number was central nervous system (CNS) tumours (26 cases observed; SIR = 1.57; [95% CI 1.02, 2.30]) in particular medulloblastoma (9 cases observed; SIR = 3.1; [95% CI 1.4, 5.9]). In a nested case–control study of the CNS tumours, we found that more cases than controls had been exposed to diagnostic X-rays, but the result was not significant. Surprisingly, for those born before term, the risk of CNS tumours increased with increasing gestational age in the nested case–control data. Our results are in line with previous evidence that children born before term are not at increased risk for childhood cancer in general. An explanation behind the excess of CNS tumours could not be identified, but the effect of diagnostic X-rays in newborns may deserve further attention.

Keywords: *childhood cancer, CNS tumours, preterm, newborn X-rays.*

Introduction

The international definition of a preterm infant is an infant born <37 weeks of gestation.[1] According to National Birth Statistics, 7% of all births in Denmark in 2001 were born preterm.[2] The number of survivors of preterm delivery has increased over the years with improved neonatal care. The causes of preterm birth have not been totally elucidated, but several risk factors have been identified such as infections, single marital status, low socio-economic status, black race, previous spontaneous abortions, *in vitro* fertilisation, multiple gestations and cigarette smoking.[1]

Preterm birth is an indicator of different exposures of the mother and suggests exposure of the infant to specific diseases and medical procedures. Thus preterm birth may be associated with subsequent development of childhood cancer. One exposure of concern is X-ray examinations, of which preterm infants often undergo a considerable number.[3] Preterm infants may be more sensitive to X-rays than infants born at term. This is particularly relevant as at present there is no threshold for a minimum dose of radiation under which there is no excess risk of cancer.[4] Several studies concerning birth-related variables and childhood cancer have investigated the effect of being born <37 weeks' gestation compared with being born at term,[5–21] but only one has reported an excess risk of cancer.[5] This was a Russian case–control study including 593 cases of various types of childhood cancer among which preterm birth was significantly associ-

ated with brain tumours only. Others have suggested that extreme preterm birth is related to hepatoblastoma.[22] On the other hand, preterm birth has been found to reduce the risk of neuroblastoma.[13,14]

Almost all previous studies on gestational age are case–control studies. We have performed a cohort study on 35 178 infants with the diagnosis immaturity as a marker of preterm delivery identified in the nationwide Hospital Discharge Register and followed them for childhood cancer in the Danish Cancer Registry.

Methods

Cohort study

The Danish National Hospital Discharge Registry (HDR), established in 1977, keeps information on about 99% of all hospitalisations in non-psychiatric hospitals in Denmark.[23] Variables registered for each hospitalisation include the personal identification number of the patient, date of admission and discharge, and up to 20 diagnoses. The unique personal identification number which is assigned at birth for each resident in Denmark ensures unambiguous linkage of information in various registers. From the identification number, date of birth and sex of the individual can be read. Diagnoses recorded were coded according to a Danish version of ICD-8[24] until 1993.

In HDR, we identified 37 889 individuals discharged with the code for immaturity (ICD-8 = 777.99, including prematurity, dysmaturity and small for dates) from 1977 to 1989. Of these, we excluded 414 (1%) with invalid identification numbers, 1632 (4%) who died at the immaturity hospitalisation, and 665 (2%) who were more than one month old at admission for immaturity. Thus, 35 178 children remained in the cohort.

Follow-up for cancer started on the first day of the month following the date of discharge with immaturity and continued until date of death, date of first primary cancer, or 31 December 1994. Dates of death were obtained by linkage to the National Death Certificate file, whereas cancer cases diagnosed during follow-up were ascertained by linkage to the Danish Cancer Registry.

Since 1943, the Danish Cancer Registry has received notifications from clinicians whenever a malignant neoplasm is diagnosed or when changes in the initial diagnosis occur. Besides malignant tumours, the Registry also gets reports of benign tumours in the nervous system. All tumours are coded according to a revised version of ICD-7,[25] and since 1978 also according to ICD-O.[26] On the basis of ICD-O codes, tumours can be categorised into diagnostic groups according to a classification scheme for childhood cancers prepared by the International Agency for Research on Cancer (IARC).[27,28] For tumours registered in 1977, the original diagnostic information on the notification forms was reviewed and an ICD-O code was assigned to each tumour as described previously.[29]

Incidence rates for first primary childhood cancer were calculated for the total population of children in Denmark (aged 0–19 years) divided into specific strata for each sex, five-year age groups and five-year calendar periods. Person-years accumulated for the cohort in each strata during follow-up were multiplied with the corresponding incidence rates to yield an expected number of cancers among children born immature, under the assumption that they experience the same cancer risk as Danish children in general. As a measure of the relative risk of childhood cancer we calculated standardised incidence ratios (SIR) as the observed number of cancers divided by the expected number and computed 95% confidence intervals [CI] assuming a Poisson distribution.

Nested case–control study

A nested case–control study was carried out for central nervous system (CNS) tumours. Of 26 cases of CNS tumours, we excluded one adenoma of the pituitary gland. For the remaining 25 tumours, we selected two controls matched on sex from the risk set of immature children alive and free of CNS tumours at the age of tumour diagnosis for the case. The medical records for the 75 children were searched at the hospital department where the child had been admitted under the diagnosis immaturity. Medical records were obtained for all 25 cases, whereas it was only possible to obtain medical records for 43 (86%) of the 50 controls (we have no reason to believe that the controls for whom the medical records could not be retrieved differed from the controls with medical records). Information on a number of variables for the child such as diagnostic X-rays during the neonatal period, birthweight, gestational age, mode of delivery and Apgar score was systematically obtained from the medical record. In addition, the medical record was reviewed for infor-

mation on the mother, such as cause of preterm birth and diagnostic and any therapeutic ionising radiation.

Odds ratios (OR) for diagnostic X-ray and perinatal characteristics were calculated from exact conditional logistic regression models. Diagnostic X-ray was entered in the model as categorical variable (yes/no). Gestational age and birthweight were entered as continuous variables, while mode of delivery (vaginal/caesarean) and Apgar score (<10/10) were entered as categorical variables. The statistical analyses were performed using LOGXACT version 2.1.

Results

Cohort study

The cohort of immature newborns consisted of slightly more boys (52%) than girls (48%). The number of hospitalised children was quite constant (on average 2850 per year) from 1980, but tended to be slightly lower the in first few years of the study period. During follow-up, a total of 387 130 person-years were accumulated, i.e. the children were on average followed until age 11 years, whereas the maximum age at the end of the study was age 18 years.

Table 1. Observed (Obs) and expected (Exp) numbers and standardised incidence ratios (SIR) of childhood cancer among 35 178 children with the diagnosis immaturity at birth during 1977–89 in Denmark

Childhood cancer	Obs	Exp	SIR [95% CI]
Leukaemias	14	19.9	0.70 [0.38, 1.18]
Lymphomas and other reticuloendothelial neoplasms	3	4.5	0.67 [0.14, 1.97]
CNS and miscellaneous intracranial and intraspinal neoplasms	26	16.6	1.57 [1.02, 2.30]
Sympathetic nervous system tumours	6	5.1	1.19 [0.43, 2.59]
Retinoblastoma	4	2.2	1.80 [0.48, 4.61]
Wilms tumour	3	3.9	0.76 [0.15, 2.23]
Hepatic tumours	1	0.7	1.42 [0.02, 7.91]
Malignant bone tumours	1	1.7	0.60 [0.01, 3.35]
Soft tissue sarcomas	3	3.4	0.87 [0.17, 2.54]
Germ-cell, trophoblastic and other gonadal neoplasms	2	1.5	1.35 [0.15, 4.89]
Carcinoma and other malignant epithelial neoplasms	1	1.7	0.60 [0.01, 3.32]
Other and unspecified malignant neoplasms	0	0.5	– –
All malignant neoplasms	64	61.8	1.03 [0.80, 1.32]

CI, confidence interval; CNS, central nervous system.

Table 2. Observed (Obs) and expected (Exp) number and standardised incidence ratios (SIR) for CNS tumours by sex, age at cancer and subtypes of tumours among 35 178 children with the diagnosis immaturity at birth during 1977–89 in Denmark

Characteristic	Obs	Exp	SIR [95% CI]
Sex			
Boys	9	8.6	1.1 [0.5, 2.0]
Girls	17	8.0	2.1 [1.2, 3.4]
Age at cancer (years)			
<1	2	1.3	1.5 [0.2, 5.4]
1–4	10	5.6	1.8 [0.9, 3.3]
5–9	9	6.4	1.4 [0.6, 2.7]
10–18	5	3.2	1.6 [0.5, 3.6]
Type of CNS tumour			
Ependymoma	2	1.4	1.5 [0.2, 5.3]
Astrocytoma	8	6.4	1.2 [0.5, 2.5]
Medulloblastoma	9	2.9	3.1 [1.4, 5.9]
Other glioma	0	0.7	– –
Miscellaneous	7[a]	5.2	1.3 [0.5, 2.8]
Total	26	16.6	1.57 [1.02, 2.30]

[a]One craniopharyngioma of the pituitary gland, one adenoma of the pituitary gland, one astrocytoma obs.pro., one medulloblastoma obs.pro., and three cases with no microscopic confirmation.
CI, confidence interval; CNS, central nervous system.

In total, there were 64 cases of childhood cancer among immature children compared with 61.8 expected (SIR = 1.03; [95% CI 0.80, 1.32]) (Table 1). The CNS tumour was the only cancer site for which we observed a significant excess (SIR = 1.57; [95% CI 1.02, 2.30]) on the basis of 26 cases against 16.6 expected. The risk was significantly twofold increased among girls, but just slightly increased among boys (Table 2). The largest excess was seen for medulloblastoma with nine cases observed vs. 2.9 expected (SIR = 3.1; [95% CI 1.4, 5.9]).

Nested case–control study

The main proportion of the controls selected at random from the cohort were born before gestational age 37 weeks and had a birthweight <2500 g ($n = 26$; 60%), whereas only one control was born <37 weeks with a birthweight >2500 g (2%). The remaining controls were born during or after week 37 of whom 7 (16%) had a birthweight <2500 g and 9 (21%) had a birthweight >2500 g.

The cause of preterm birth was idiopathic in 45% of cases and 78% of controls. The second most common cause among cases was bleeding (27% in cases and 7% in controls).

There were more cases than controls who had been exposed to diagnostic X-rays, although the risk was not significantly elevated (OR = 1.3; [95% CI 0.4, 4.0]) (Table 3). There was a borderline significant effect of increasing gestational age (per week OR = 1.1; [95% CI 1.0, 1.3]), but no significant effect of birthweight, mode of delivery or Apgar score. When the effect of diagnostic X-ray was adjusted for gestational age, the OR increased to 2.2, but the risk was still not significantly elevated [95% CI 0.6, 8.8]. When cases and controls with gestational age ≥37 weeks or birthweight at or above 2500 g were excluded, these results did not change substantially except for the risk for diagnostic X-ray adjusted for gestational age (OR = 1.0; [95% CI 0.2, 5.8]). The effect of X-ray adjusted for gestational age differed among those with gestational age <37 weeks (OR = 0.7; [95% CI 0.1, 6.3]) and those with gestational age ≥37 weeks (OR = 4.9; [95% CI 0.5, 254]) (test for difference $P = 0.47$). The effect of gestational age adjusted for radiation also differed for those with gestational age <37 weeks (per week OR = 1.4; [95% CI 1.0, 2.2]) and those with gestational age ≥37 weeks (per week OR = 0.7; [95% CI 0.4, 1.2]) (test for difference $P = 0.11$).

Among those who had been exposed to diagnostic X-rays, two cases had X-rays to the brain (one case had several CT scans – the first when 6 days old – due to cerebral damage after neonatal asphyxia, and one case had X-rays when 6 days old due to head trauma), whereas none of the controls had received X-rays to the brain. For those remaining, the X-rays had been given to the thorax (9 cases and 15 controls) and abdomen (2 cases and 3 controls). Some cases and controls had more than one X-ray examination to the same location (9 cases and 9 controls) or had X-rays to different locations (2 cases and 3 controls). None of the mothers of cases and controls had any recordings of therapeutic or diagnostic ionising radiation during the pregnancy.

Table 3. Odds ratios (OR) for CNS tumours by perinatal characteristics and diagnostic X-rays on the basis of 25 cases and 43 randomly selected controls within the cohort of 35 178 children with the diagnosis immaturity at birth during 1977–89 in Denmark

Characteristics	Cases (%)	Controls (%)	Crude OR [95% CI]	Adjusted OR [95% CI]
Birthweight (g)				
<1500	3 (12)	7 (16)		
1500–2499	12 (48)	26 (60)	1.2[a] [0.9, 1.7]	
2500–3499	7 (28)	7 (16)		
≥3500	2 (8)	3 (7)		
Unknown	1 (4)	0 (0)		
Gestational age (weeks)				
27–32	3 (12)	13 (30)	1.6[b] [1.1, 2.6]	1.4[b,c] [1.0, 2.2]
33–36	8 (32)	14 (33)		
37+	13 (52)	16 (37)	0.7[b] [0.3, 1.2]	0.7[b,c] [0.4, 1.2]
Unknown	1 (4)	0 (0)		
Mode of delivery				
Vaginal	15 (60)	33 (77)	1.0 Reference	
Caesarean	10 (40)	10 (23)	2.3 [0.7, 9.2]	
Apgar score at one minute				
≤8	9 (36)	12 (28)	1.7 [0.6, 5.5]	
9	6 (24)	8 (19)		
10	10 (40)	23 (53)	1.0 Reference	
Diagnostic X-Rays				
Yes	11 (44)	15 (35)	1.3 [0.4, 4.0]	2.2[d] [0.6, 8.8]
No	14 (56)	28 (65)	1.0 Reference	1.0 Reference

[a]Per 500 g.
[b]Per week.
[c]Adjusted for diagnostic X-rays.
[d]Adjusted for gestational age. One unexposed case not included due to missing gestational age.
CI, confidence interval; CNS, central nervous system.

Discussion

Children who received the diagnosis immaturity had no overall excess risk of childhood cancer. The increased relative risk of CNS tumours was of borderline significance elevated due to an excess of medulloblastoma. In our nested case–control study, cases with CNS tumours were more likely to have received diagnostic X-rays than controls but the OR for this exposure was not significantly elevated.

Our study covered almost all births in Denmark during 1977–89, as only 0.8% of children were born at home during this period[30] and not included in the data from the Hospital Discharge Register. Recall bias was avoided by use of data from the Hospital Discharge Register and medical records. The criteria for using the diagnosis immaturity in the Discharge Register are not well-defined but, among the controls in the nested case–control study, 63% were born before week 37 of gestation and 76% had low birthweight (<2500 g), whereas 21% apparently had signs of immaturity despite being born at term with a normal birthweight. By use of the Danish Cancer Registry, we had access to high-quality data on childhood cancer classified according to the IARC scheme. Even though follow-up was only extended until 1994, we had complete ascertainment of the risk of cancer among the youngest children aged 0–4 years. In the cohort study, we investigated whether immaturity at birth is associated with cancer, whereas the nested case–control study was set up to reveal which characteristics of immaturity caused the excess of CNS tumours found in the cohort study. However, lack of statistical power prevented us from screening a wide range of potential risk factors associated with immaturity at birth.

A number of reports have shown no association between gestational age <37 weeks and childhood cancer overall[7,11] or leukaemia.[7–10] All were case–control studies including between 33 and 1842 cases with birth characteristics obtained from birth records[7–9,11] or telephone interviews with the parents.[10] Our results are in support of these studies that preterm birth is not generally associated with childhood cancer nor associated with leukaemia. Neuroblastoma has been of particular interest in relation to pre- and perinatal characteristics, because it is one of the most common tumours diagnosed in children of less than 1 year of age.[31] Case–control studies from Texas[14] and New York State[13] showed a significantly decreased risk of neuroblastoma on the basis of 157 and 155 cases, respectively, while a third case–control study from the US and Canada[12] with 504 cases showed a decreased risk for gestational age between 33 and 36 weeks but not for gestational age <33 weeks. We found no evidence of a decrease in risk for preterm birth on the basis of 6 observed and 5.1 expected cases of neuroblastoma. We had no possibility of identifying the subgroup of children who were born extremely preterm, but we found no indication of an increase in hepatoblastoma as reported earlier,[22] as only one case of hepatic cancer was found.

As mentioned above, our cohort included a substantial proportion of children with birthweight <2500 g. A large number of studies have investigated the importance of birthweight in respect to childhood cancer. However, these studies mostly found no significant association with low birthweight[32] with a few exceptions.[5,14,16,33] A recent meta-analysis based on 15 studies has shown a dose–response relationship between birthweight and acute lymphatic leukaemia with a significant increase of 1.15 for each 1000 g increase in birthweight.[34] In line with this, we observed fewer cases of leukaemia than expected, and in the nested case–control study, there was a tendency towards increasing risk of CNS tumours with increasing birthweight. A Russian study has shown excesses of leukaemia and lymphoma among children with low birthweight, but only among those born at term.[5] A corresponding finding for neuroblastoma was reported in a study from Texas.[14]

CNS tumours were the only cancer type in our study for which the observed number of cases deviated significantly from the expected number. Of eight previous studies[5,6,16–21] only one showed an excess of CNS tumours among children born before term.[5] The case–control studies showing no association included between 83 and 1218 cases with CNS tumours, and gestational age was obtained through birth records[17,18,21] or interviews.[6,16,20] One cohort study has been published so far and this also showed no association. The study included 459 CNS tumours among 1489 297 children from Norway for whom gestational age was ascertained through a Birth Registry.[19] The excess of CNS tumours among preterm births was found in a population-based case–control study from Moscow which included 57 brain tumours and data on exposures from face-to-face interviews with parents.[5] The OR for preterm birth was 13.3 with a 95% CI of 1.5 to 301.2. No definition of preterm birth was given. Our risk estimate of 1.6 was more moderate and of border-

line significance. The largest excess was seen for medulloblastoma, but none of the previous studies reported any significantly increased risk for medulloblastoma[15,16,19,21] or primitive neuroectodermal tumours[17,20] after preterm birth. In the nested case–control study, we unexpectedly found that the risk of CNS tumours increased with increasing gestational age for those born preterm.

The exposure of main interest in our nested case–control study of the CNS tumours was X-ray examinations of the newborn child. Therapeutic radiation of the child is one of the few established risk factors for childhood brain cancer,[35] whereas the evidence concerning diagnostic radiation of the child is inconsistent; two previous studies showed significant positive associations[36,37] whereas six studies did not.[6,16,38–41] The discrepancy may partly be explained by differences in the dose applied, as in one of the two studies showing a positive association all children were exposed before 1964 when the average dose applied was higher. However, gestational age was not taken into consideration in these studies, and children born preterm may be more susceptible to radiation than children born at term. This is supported by observations that diagnostic radiation *in utero* increases the risk of CNS tumours although this has been the subject of great controversy.[42]

On the other hand, radiation-induced effects are not specific for CNS tumours but seem to apply to all types of childhood cancer[42] for which we saw no excess among the immature cohort. Nevertheless, in the nested case–control study, we found that cases were more likely to have had X-ray examinations than controls – though only among those born at term – but none of the ORs attained statistical significance. Also, the lack of increase in risk by increasing age at diagnosis does not add strong support for diagnostic X-rays as the underlying cause of the excess of CNS tumour, as it would presumably take time for a radiation-induced cancer to develop. Two cases and none of the controls had X-ray examinations of the brain. None of the mothers of cases and controls had any recordings of therapeutic or diagnostic ionising radiation during the pregnancy, but recordings of these exposures may not have been complete in the obstetric medical record.

In line with previous reports, we found that children born before term are not at increased risk for developing childhood cancer in general. With respect to specific types of cancer, CNS tumour was the only cancer type for which significant increase in risk was seen in particular with respect to medulloblastoma. X-ray examinations were more common in CNS tumour cases than controls, but the small number of cases precluded any firm conclusion.

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